REMARKS

Status of the Claims

Claims 2, 3, 5 - 13, 26 - 34, 36, 83 - 85 and 89 - 98 are pending. Claims 83 - 85 and 87 are withdrawn from further consideration as being drawn to a nonelected invention. Thus, Claims 2, 3, 5 - 13, 26 - 34, 36 and 89 - 98 are under examination. With this Amendment, Claim 2 is being amended. The amendment of Claim 2 and the various rejections raised in the Office Action are discussed in more detail below.

Claim Amendments

Claim 2 has been amended to delete "116" and insert "109" to correct an obvious typographical error. Support for the amended is found in the specification at paragraph [0073]. Applicants assert that no new matter has been introduced by the present amendment.

Information Disclosure Statement

Applicants acknowledge receipt of the initialed information disclosure sheet submitted on 9/15/2003.

Rejection Under 35 U.S.C. § 112, Second Paragraph: Indefiniteness

Applicants acknowledge that the rejection of claims 1 - 2, 4, 26 - 27, 29, 36, 88 - 90 and 95 (and claims dependent thereon) as being indefinite has been withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

A. Claims 2 - 3, 5 - 13, 26 - 34, 36, 89 - 90 and 93 - 98 are fully supported by the specification.

Claims 2 - 3, 5 - 13, 26 -34, 36, 89 - 90 and 93 - 98 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to be described in the specification. Applicants traverse the rejection.

The Patent Office alleges that new matter was introduced into the claims by the amendments filed on 6/16/06. Applicants respectfully disagree and provide the following table showing the amended claims and the corresponding support found in the specification.

Claim	Specification
2. A method of increasing the secretion of a heterologous protein in a eukaryotic cell comprising inducing an unfolded protein response (UPR) by increasing the presence of a HAC1 UPR-modulating protein in said eukaryotic cell, comprising transforming the eukaryotic cell with a nucleic acid encoding the HAC1 UPR-modulating protein comprising a DNA binding domain having at least 90% sequence identity to a DNA binding domain of a) amino acid residues 84 – 147 of SEQ ID NO: 5; b) amino acid residues 53 – 116 of SEQ ID NO: 6 or c) amino acid residues 45 – 109 of SEQ ID No:19, and increasing secretion of the heterologous protein relative to secretion of the heterologous protein in a parental cell.	[0056] Provided herein are methods and compositions for increasing the secretion of a protein in a cell comprising inducing an elevated unfolded protein response (UPR). [0013] [...] [T]he HAC1 protein is increased in a cell by transformation of said cell by a nucleic acid comprising a UPR inducing form of a HAC1 recombinant nucleic acid. [0072] [...] [T]he HAC1 protein provided herein comprises a DNA binding domain that has at least 70% similarity to the DNA binding domain set forth in FIG. 10. More preferably, the similarity is at least 70%, more preferably at least 80%, more preferably at least 90%, and more preferably at least 95% or 98%. In another embodiment, identity is substituted for similarity [0073] Embodiments of a DNA binding region are shown approximately at amino acids 84-147 of the T. reesei protein shown in FIG. 10, approximately at amino acids 53-116 of the A. nidulans protein shown in FIG. 10 and approximately amino acids 45-109 of the A. niger protein shown in FIG. 28.
26. The method of Claim 2 wherein said eukaryotic cell is selected from the group consisting of *Aspergillus*, *Trichoderma*, *Saccharomyces*, *Schizosaccharomyces*, *Kluyveromyces*, *Pichia*, *Hansenula*, *Fusarium*, *Neurospora*, and *Penicillium*.	[0092] The cell in which the proteins are secreted is any cell having an upregulated protein response. Preferably, the host to be transformed with the genes of the invention can be any eukaryotic cell suitable for foreign or endogenous protein production, e.g., any *S. cerevisiae* yeast strain, (e.g., DBY746, BMA64-1A, AH22, S150-2B, GYPY55-15bA, vtt-a-63015) any Trichoderma spp. such as *T. longibrachiatum* and the *T. reesei* strains derived from the natural isolate QM6a, such as RUTC-30, RL-P37, QM9416 and VIT-D-79125, any Kluyveromyces spp/. Sch. pombe, H. polymorpha, Pichia, Aspergillus, Neurospora, Yarrowia, Fusarium, Penicilium spp. or higher eukaryotic cells.
27. The method of Claim 2 wherein said eukaryotic cell is a yeast cell.	
36. The method of Claim 2 wherein said eukaryotic cell is a mammalian cell.	[0093] Examples of mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36:59 (1977)); Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77:4216 (1980)); mouse sertoli cells (TM4, Mather, Biol. Reprod., 23:243-251 (1980)); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2, HB 8065); and mouse mammary tumor

	(MMT 060562, ATCC CCL51).
89. The method of Claim 2 wherein said UPR-modulating protein comprises a DNA binding domain that has at least 90% identity to the DNA binding domain of a) amino acid residues 84 – 147 of SEQ ID NO: 5 or b) amino acid residues 53 – 116 of SEQ ID NO: 6.	[0072] [...] [T]he HAC1 protein provided herein comprises a DNA binding domain that has at least 70% similarity to the DNA binding domain set forth in FIG. 10. More preferably, the similarity is at least 70%, more preferably at least 80%, more preferably at least 90%, and more preferably at least 95% or 98%. In another embodiment, identity is substituted for similarity.
90. The method of Claim 2 wherein said UPR-modulating protein comprises a DNA binding domain that has at least 95% identity to the DNA binding domain of a) amino acid residues 84 – 147 of SEQ ID No: 5 or b) amino acid residues 53 – 116 of SEQ ID No: 6 or c) amino acid residues 45 – 116 of SEQ ID No:19.	[0072] [...] [T]he HAC1 protein provided herein comprises a DNA binding domain that has at least 70% similarity to the DNA binding domain set forth in FIG. 10. More preferably, the similarity is at least 70%, more preferably at least 80%, more preferably at least 90%, and more preferably at least 95% or 98%. In another embodiment, identity is substituted for similarity.
95. The method of Claim 2, wherein the eukaryotic cell is a Trichoderma or Aspergillus fungal cell, the UPR-modulating protein comprising a DNA binding domain has at least 90% sequence identity to the DNA binding domain of a) amino acid residues 84 – 147 of SEQ ID NO: 5 or b) amino acid residues 53 – 116 of SEQ ID NO: 6 and the heterologous protein is selected from the group consisting of proteases, cellulases, glucoamylases, alpha amylases and combination thereof.	[0072] [...] [T]he HAC1 protein provided herein comprises a DNA binding domain that has at least 70% similarity to the DNA binding domain set forth in FIG. 10. More preferably, the similarity is at least 70%, more preferably at least 80%, more preferably at least 90%, and more preferably at least 95% or 98%. In another embodiment, identity is substituted for similarity. [0091] In another embodiment, the protein of interest is selected from the group consisting of lipase, cellulase, endo-glucosidase H, protease, carbohydrase, reductase, oxidase, isomerase, transferase, kinase, phosphatase, alpha-amylase, glucoamylase, lignocellulose hemicellulase, pectinase and ligninase.
96. The method of Claim 95, wherein the eukaryotic cell is a Trichoderma cell and the UPR-modulating protein comprises a DNA binding domain that has at least 95% sequence identity to the DNA binding domain of a) amino acid residues 84 – 147 of SEQ ID NO: 5 or b) amino acid residues 53 – 116 of SEQ ID NO: 6.	[0092] The cell in which the proteins are secreted is any cell having an upregulated protein response. Preferably, the host to be transformed with the genes of the invention can be any eukaryotic cell suitable for foreign or endogenous protein production, e.g., any S. cerevisiae yeast strain, (e.g., DBY746, BMA64-1A, AH22, S150-2B, GYPY55-15bA, vtt-a-63015) any Trichoderma spp. such as T. longibrachiatum and the T. reesei strains derived from the natural isolate QM6a, such as RUTC-30, RL-P37, QM9416 and VIT-D-79125, any Kluyveromyces spp/..Sch. pombe, H. polymorpha, Pichia, Aspergillus, Neurospora, Yarrowia, Fusarium, Penicilium spp. or higher eukaryotic cells. [0072] [...] [T]he HAC1 protein provided herein comprises a DNA binding domain that has at least 70% similarity to the DNA binding domain set forth in FIG. 10. More preferably, the similarity is at least 70%, more preferably at least 80%, more preferably

	at least 90%, and more preferably at least 95% or 98%. In another embodiment, identity is substituted for similarity
97. The method of Claim 95, wherein the eukaryotic cell is an Aspergillus cell and the UPR-modulating protein comprises a DNA binding domain that has at least 95% sequence similarity to the DNA binding domain of a) amino acid residues 84 – 147 of SEQ ID NO: 5; b) amino acid residues 53 – 116 of SEQ ID NO: 6.	[0092] The cell in which the proteins are secreted is any cell having an upregulated protein response. Preferably, the host to be transformed with the genes of the invention can be any eukaryotic cell suitable for foreign or endogenous protein production, e.g., any S. cerevisiae yeast strain, (e.g., DBY746, BMA64-1A, AH22, S150-2B, GYPY55-15bA, vtt-a-63015) any Trichoderma spp. such as T. longibrachiatum and the T. reesei strains derived from the natural isolate QM6a, such as RUTC-30, RL-P37, QM9416 and VIT-D-79125, any Kluyveromyces spp/. Sch. pombe, H. polymorpha, Pichia, Aspergillus, Neurospora, Yarrowia, Fusarium, Penicilium spp. or higher eukaryotic cells. [0072] [...] [T]he HAC1 protein provided herein comprises a DNA binding domain that has at least 70% similarity to the DNA binding domain set forth in FIG. 10. More preferably, the similarity is at least 70%, more preferably at least 80%, more preferably at least 90%, and more preferably at least 95% or 98%. In another embodiment, identity is substituted for similarity

In view of the foregoing, Applicants submit that the pending claims are described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Accordingly, Applicants request withdrawal of rejection of Claims 2 - 3, 5 -13, 26 - 34, 36, 89 - 90 and 93 - 98 under 35 U.S.C. §112, first paragraph.

B. Claims 2 - 3, 5 - 13, 26 - 34, 36 and 89 - 98 comply with the written description requirement

Claims 2 - 3, 5 - 13, 26 – 34, 36 and 89 -98 stand rejected under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. The rejected claims allegedly contain subject which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse.

In particular, the Patent Office alleges that the rejected claims do not provide any structural information with regards to 1.) the portions of the DNA binding domains which are critical for HAC1

UPR-modulating function 2.) which recited DNA binding domains-containing sequences would functional as HAC1 UPR-modulating proteins, and 3.) heterologous proteins whose secretion can be increased by such method. Further the Patent Office states that claims comprise a set of nucleic acids sequences which encode amino acid sequences that are defined by the function of the encoded protein. (*See*, Office Action, page 7). Applicants respectfully disagree.

First, Applicants submit that the written description requirement is not based solely on structural information. In Enzo Biochem, Inc. v. Gen-Probe Inc, 323 F.3d 956 (Fed. Cir. 2002) the court stated that: The written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." Enzo Biochem, 323 F.3d at 964 (citing Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1 "Written Description Requirement, 66 Fed. Reg. 1099, 1106 (January 5, 2001)).

Secondly, Applicants submit that the claims explicitly recite sufficiently detailed relevant identifying characteristics to comply with written description requirement. Applicants believe that a brief discussion on what was known in the art with respect to HAC1 structure and function will be helpful. As described in the Background of the Invention, it has been reported that the yeast transcription factor mediating the UPR induction of the chaperone and foldase genes is the HAC1 protein (Cox and Walter, 1996, Cell 87:391-404, Sidrauski *et al.*, 1996, Cell 87:405-413). HAC1 belongs to the bZIP family of transcription factors, having a basic DNA-binding region and a leucine zipper dimerization domain. The binding of the HAC1 protein to the UPR element of ER-protein gene promoters has been demonstrated (Mori *et al.*, 1998, J. Biol. Chem. 273: 9912-9920). Further the action of the HAC1 protein is regulated by the amount of HAC1 in cells. (*See*, Specification, paragraph [0008]).

The Patent Office asserts that the rejected claims comprise a set of nucleic acid sequences which encode amino acids that are defined by the function of the encoded proteins. (*See*, Office Action, pages 7-8). Applicants respectfully disagree. The pending claims are directed, in part, to methods of increasing the secretion of a heterologous protein in a eukaryotic cell with specific amino acid sequences that are defined by both structure and function. For example, independent Claim 2, is directed in part a method that include nucleic acid encoding the HAC1 UPR-modulating

protein comprising a DNA binding domain having at least 90% sequence identity to a DNA binding domain of a) amino acid residues 84 -147 of SEQ ID NO: 5; b) amino acid residues 53 -116 of SEQ ID NO: 6 or c) amino acid residues 45 – 109 of SEQ ID NO:19.

The Patent Office asserts that the claims do not provide any structural information with regard to the portion of a DNA binding domains which are critical for HAC1 UPR-modulating function, or motifs which would allow one skilled in the art to identify any nucleic acid sequence encoding a HAC1 UPR-modulating proteins with DNA binding domains. (*See*, Office Action, page 9). Applicants respectfully disagree. The specification provides the amino acid sequence of HAC1 proteins from four different species of yeast or filamentous fungi, including *Saccharomyces cerevisiae*, *Trichoderma reesei*, *Aspergillus niger* and *Aspergillus nidulans*. In addition, the specification provides sequence alignments showing conserved regions of HAC1 proteins. For example, FIG. 10 depicts the amino acid sequence alignment of the *T. reesei* HAC1, *A. niduans* hacA and *S. cerevisiae* HAC1 proteins. The identical amino acids in the HAC1 proteins are shown by asterisks and similar ones by dots. As described in the specification, yeast HAC1 is homologous to the other sequences at the DNA binding domain area. Likewise, FIG. 28 depicts amino acid sequences of the HAC1 protein (SEQ ID NO: 19) from *Aspergillus niger*. The DNA binding region is shown at approximately amino acids 45-109 of the *A. niger* protein shown in FIG. 28. As described in the specification, HAC1 homologs will have DNA binding domains which can be identified by activity or by alignment to the binding domains in provided in the specification.

The Patent Office asserts that the claims do not provide any structural information with regard to the heterologous proteins whose secretion can be increased by such methods. Applicants respectfully disagree. First, the specification describes that the heterologous proteins can include for example, a lipase, cellulase, endo-glucosidase H, protease, carbohydrase, reductase, oxidase, isomerase, transferase, kinase, phosphatase, alpha-amylase, glucoamylase, lignocellulose hemicellulase, pectinase, ligninase, vaccines, cytokines, receptors, antibodies, hormones, and factors including growth factors. (*See*, specification, paragraphs [0090] - [0091]). In addition, the specification describes several examples of heterologous proteins whose secretion is increased. Example 1 shows constitutive induction of the unfolded protein response in *Saccharomyces cerevisiae*, wherein the heterologous α-amylase produced by each of the HAC1 transformants were higher than the amounts produced by control cells. The average production level amylase in HAC1 transformants was 70% higher in the end of the cultivation than the control

(FIG. 2). In addition, endogenous invertase production of the HAC1 transformants was about 2 times higher than that of the control (FIG. 3).

The effect of HAC1 disruption on the production of two heterologous proteins, the *Bacillus amyloliquefaciens* α-amylase and the *Trichoderma reesei* endoglucanase EGI, is described in Example 2. The HAC1 disruptant strain produced less than 10% of the alpha-amylase amount produced by the wild type control strain (FIG. 4). The production of the endoglucanase EGI of the HAC1 disruptant was about 50% of the level produced by the parental strain (FIG. 5). Example 7 shows expression in yeast of the *Trichoderma* HAC1 cDNA (pMS132) on protein expression in a yeast strain producing heterologous α-amylase described. Again the α-amylase (FIG. 17) and invertase (FIG. 18) production of the HAC1 transformants was higher than that of the control cells. Example 13 shows yet another example of the effect of HAC1 overexpression on heterologous protein production. As shown in FIG. 30, the HAC1 transformants produced 1.3-2.8 fold more chymosin than the parental strain. Likewise, the HAC1 transformants produced 2 to 5.4 fold more laccase than the parental strain (FIG. 31). These results demonstrate that overexpression of HAC1 enables production of higher levels of endogenous proteins as well as a variety of heterologous proteins.

The Patent Office asserts that the examples are only representative of four HAC1 UPR-modulating proteins comprising a DNA binding domain as recited in claim 2 and that the results are not predictive of any nucleic acid sequences encoding an amino acid sequences comparing a HAC1 UPR-modulating protein comprising a DNA binding domain with 90% identity to a DNA binding domain set forth in claim 2. (*See*, Office Action, page 9). Applicants respectfully disagree. The Patent Office relies on Roberson *et al.* (Bio/Technology 12: 381 – 384, 1994) to show that allegedly the prior art does not appear to offset the deficiency of the instant application in that it does not describe any other UPR-modulating proteins isolated from yeast or filamentous fungi comprising a DNA binding domain set forth in claim 2. Roberson *et al.* teaches that overexpression of protein disulfide isomerase (PDI) results in higher expression of human platelet derived growth factor. That Roberson *et al.* does not describe HAC1 or any other UPR-modulating proteins that can also increase the secretion of a heterologous protein, as the Patent Office asserts, does not affect the allegedly deficiencies in the instant application. To the contrary, Roberson *et al.* states that that the work [on PDI over expression] provides an "example of successful engineering the

eukaryotic secretory pathway for enhanced production characteristics, and serves as paradigm for rationally improving expression systems by molecular genetics. (*See*, Robinson *et al.*, pg. 381).

In sum, the Patent Office alleges that given the genus of nucleic acids which can encode the amino acid molecules encompassed by the rejected claims, the skilled artesian would not be able to describe the broadly claimed genus of UPR-modulating proteins isolated form yeast or filamentous fungi comparing the a DNA binding domain as set forth in Claim 2, such that the secretion of any heterologous protein is increased. (*See*, Office Action, page 10). Applicants respectfully disagree. As described above, Applicants submit that the genera of nucleic acids which can encode the amino acid molecules encompassed by the rejected claims, and the heterologous proteins, are supported by the specification as filed. Simply because the Claims arguably encompass a large number of sequences and heterologous proteins, is not a proper ground for rejection, as the present specification clearly provides the teaching necessary to obtain the nucleic acids encoding the HAC1 UPR-modulating protein comprising the DNA binding domain to the recited sequences, and increasing the secretion of heterologous proteins. Applicants respectfully submit that the specification, as described above, described the genus of nucleic acids and heterologous proteins to satisfy the written description requirement. For the reasons discussed above, the specification satisfies the written description requirement of 35 U.S.C. §112, first paragraph, and Applicants respectfully request withdrawal of this rejection.

C. Claims 2 - 3, 5 - 13, 26 - 34, 36, 89 - 98 are enabled.

Claims 2 - 3, 5 -13, 26 - 34, 36, and 89 – 98 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement. Applicants respectfully traverse.

The Patent Office states that the specification does not reasonably provide enablement for *A. nidulans* HAC1 or any other HAC1 UPR-modulating protein comprising a DNA binding domain set forth in Claim 2. Applicants respectfully disagree. Applicants acknowledge the Patent Office's statement that the specification is enabling for HAC1/hacA isolated from *S. cerevisiae*, *T. reesei*, and *A. niger* var. *awamori* used in conjunction with certain secreted heterologous proteins.

The first paragraph of 35 U.S.C. § 112 requires, *inter alia*, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Section 112, first paragraph, has been interpreted to require that the specification teach those in the art to make and use the invention without 'undue experimentation.' (*See*, *In re* Wands, 858

F.2d 731, 737 (Fed. Cir. 1988)). Enablement is considered in view of Wands factors (MPEP 2164.01). The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, and the specification need not disclose what is well known in the art. (*See*, Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463 (Fed. Cir. 1984) (citing In re Myers, 410 F.2d 420, (CCPA 1969)). "A patent need not teach, and preferably omits, what is well known in the art." Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987). "Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be." In re Gay, 309 F.2d 769, 774, (CCPA 1962).

Nature of the invention: The Patent Office alleges that the invention is complex in that the claims are directed in part to increasing the secretion of a heterologous protein by increasing the presence of the recited UPR-modulating protein. The Patent Office alleges that increasing the presence of a UPR-modulating protein is not simply a matter of expressing any form of a UPR-modulating protein (*See*, Office Action, page 12). The Patent Office states that endogenous HAC1 protein is expressed after an intron is spliced from the mRNA, and the cell maintains a balance of spliced and unspliced transcripts, and the difference the amino acids between the induced and uniduced HAC1 protein, relying on the on the teaching of Shamu, Current Biology: R121-R123 (1998).

Applicants agree that increasing the presence of a UPR-modulating protein is not simply a matter of expressing any form of a UPR-modulating protein. In fact, the Background of the Invention describes in detail what was known to one skilled in the art at paragraph regarding the form the UPR-modulating protein. (*See*, Specification, paragraph [0008]). As described, in uninduced conditions the intron present in the HAC1 gene close to the translation termination codon is not spliced off, and this intron prevents the formation of HAC1 protein by preventing the translation of the mRNA (Chapman and Walter, 1997, Curr. Biol. 7,850-859, Kawahara *et al.*, 1997, Mol. Biol. Cell 8, 1845-1862). When UPR is induced, the intron is spliced and the mRNA is translated to form HAC1 protein that activates the promoters of its target genes. The HAC1 intron is spliced by an mechanism not currently described for any other system, involving the RNAse activity of the IRE1 protein and a tRNA ligase (Sidrauski and Walter, 1997, Cell 90, 1031-1039, Gonzales et al., 1999, EMBO J. 18, 3119-3132, Sidrauski *et al.*, 1996, Cell 87, 405-413). The unfolded

protein response can be induced constitutively in yeast by transformation with a UPR inducing version of the HAC1 gene.

The pending application takes into account the UPR inducing form of a HAC1 protein. For example, Claim 2 recites in part: "inducing an unfolded protein response (UPR) by increasing the presence of a HAC1 UPR-modulating protein in said eukaryotic cell, comprising transforming the eukaryotic cell with a nucleic acid encoding the HAC1 UPR-modulating protein comprising" the recited DNA binding domains. The fact that Applicants do not explicitly provide examples regarding every polynucleotide encompassed by the present invention does not render the present claims unpatentable. Techniques were well known in the art on how to compare the protein with other proteins and have a reasonable expectation of success. Beginning with the sequence provided, see for example figures

10 and 28, one of skill in the art would know how to proceed if they wanted to generate additional HAC1 proteins and variants – compare the sequence with known related sequences, identifying in the three-dimensional structure at least one structural part of the parent HAC1; modifying the nucleic acid sequence encoding the parent HAC1 to produce a nucleic add sequence encoding a variant of the parent HAC1 having a deletion, insertion, or substitution of one or more amino acids at a position corresponding to said structural part; and expressing the modified nucleic acid sequence in a host cell. All of the methods and techniques are described in the specification or were familiar to the skilled artisan and are not required to be taught in the specification. Simply requiring additional testing does not render the claims non-enabled .

Guidance of the specification/the existence of working examples: The specification teaches in part that that secretion of a heterologous protein can be increased by expression of a UPR inducing form of a HAC1 recombinant nucleic acid. The Patent Office states that there are two working examples in the specification of methods for increasing the secretion of a heterologous protein comprising inducing a UPR by increasing the presence of a UPR-modulating protein isolated from yeast and filamentous fungi. The Patent Office alleges that the breadth of the claims is unsupported because there are not enough examples. With respect to Examples it is long standing patent law that examples are no mandatory for a patent application. Not with standing this, Applicants submit that the Examples, described in more detail below provide ample exemplification to allow one skilled in the art to make and use the invention.

For instance, Example 7 shows that the heterologous expression of α-amylase is increased in yeast transformed with *Trichoderma* HAC1 cDNA. In addition, Example 9 shows the effect of *T. reesei* HAC1 mutation on heterologous CBHI-chymosin production. In yet another eukaryotic cell, *A. niger* var. awamori, overexpression of hacA resulted in higher levels of two secreted proteins, chymosin and laccase. Also, Example 1 shows that heterologous expression of α-amylase was increased in yeast expressing truncated HAC1.

Predictability of the art and the amount of experimentation: The Patent Office alleges that Valkonen *et al.* (Applied and Environmental Microbiology 69 (4) 2065-2072, (2003)) teach that over-expression of yeast HAC1 or *T. reesei* hac1 can lead to increased secretion of heterologous α-amylase, but not heterologous endoglucanase. (*See*, Office Action, page 5). While Valkonen did show that HAC1 affects production of both a native protein, invertase and a foreign protein, α-amylase, that fact that they could not detect improved production of endoglucanase EGI, does not render the claims non-enabled.

Consequentially, Valkonen *et al.* supports the full scope of the claims and contradicts the Patent Office's position. Valkonen states that "microarray experiments with S. *cerevisiae* have shown that the UPR pathway regulates the transcription of about 380 genes though the action of Hac1p." (See Valkonen *et al.*, pg. 2070). In addition, as described in Valkonen *et al.*, disruption of HAC1 caused a decrease in the secretion of both α-amylase and endoglucanase EGI were clearly reduced (FIG.1B and D). These results suggest that HAC1 is involved in secretion of these proteins and that UPR induction may be beneficial for the "production of these proteins and **foreign proteins in general**". (See Valkonen *et al.*, pg. 2069). The difference in the amount of α-amylase and endoglucanase EGI secretion may be attributed to the fact that endoglucanase EGI is "retained in the membranous intracellular fraction at early stages of culture". (See, Valkonen *et al.*, pg. 2071). In contrast, in the case of α-amylase, 70% of the protein produced is secreted, whereas only 30% is associated with cells" (See, Valkonen *et al.*, pg. 2071). Applicants submit, that simply requiring additional testing, the methods of which are provided in the specification, does not render the claims non-enabled.

In view of the foregoing, the Patent Office has not advanced a sufficient basis to establish a *prima facie* case of non-enablement and Applicants respectfully submit that the written description requirement is met. Accordingly, withdrawal of the rejection under 35 U.S.C. §112, first paragraph is requested.

Rejection under 35 U.S.C. §102(b):

Applicants acknowledge that the rejection of claims 1 - 2, 4 - 7, 26 - 28 and 86 - 90 as anticipated by Clarke *et al.* (J. Cell. Bioch. Suppl,) as evidenced by Shamu (Current Biology: R121-R123 (1998)) has been withdrawn.

Conclusion

In light of the above amendments, as well as the remarks, Applicant believes the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7620.

Respectfully submitted,

Michael F. Kolman
Reg. No. 54,234

Dated: January 16, 2007

Genencor, a Danisco division.
925 Page Mill Road
Palo Alto, CA 94304-1013
Tel: (650) 846-7614
Fax: (650) 845-6504